

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DIPROPYL ISOCINCHOMERONATE

Chemical Code # 000681, Tolerance # 50225
SB 950 # 300

October 8, 1987
Revised: 7/27/88, 8/16/89, 2/22/91, 9/15/95

I. DATA GAP STATUS

Combination, rat: No data gap, possible adverse effect
(chronic/onco)

Chronic dog : No data gap, no adverse effect

Onco mouse : No data gap, possible adverse effect

Repro rat : No data gap, no adverse effect

Terato rat : No data gap, no adverse effect

Terato rabbit : No data gap, no adverse effect

Gene mutation : No data gap, no adverse effect

Chromosome : No data gap, no adverse effect

DNA damage : No data gap, no adverse effect

Neurotox : Not required at this time

-----**Note, Toxicology**
one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

File name : T950915

Revised: Kishiyama, Gee, 7/27/88; Chernoff, 8/16/89; Kishiyama & Silva, 2/22/91; Kishiyama & Silva, 9/15/95.

Record numbers through volume 50225-017/111269 listed by the Pesticide Registration Library have been rectified with those listed in the Toxicology Summary.
Toxicology one-liners are attached.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY SUMMARY

COMBINATION (Chronic/Oncogenicity), RAT

Subchronic Study:

012, 016 093435, 114161 "13 Week Dietary Range-Finding Toxicity Study in Rats", (M. Blair, International Research and Development Corporation, Laboratory Project I.D. 551-002, 10/24/91 [amended]). MGK* Repellent 326 (99.4% pure) was admixed with the feed at concentrations of 0, 125, 250, 500, 1000, or 2000 mg/kg/day for 10 Charles River CD* rats/sex/group for 13 weeks. Volume/record #: 016/114161 contained the chemical analysis of the test material. NOEL = 500 mg/kg (Mortality in females occurred at increased rate at 2000 mg/kg. Both sexes showed increased clinical signs (decreased defecation, labored breathing, hunched posture--females only) at 2000 mg/kg. Both sexes at ≥ 1000 mg/kg had decreased body weight and decreased food consumption, as well as hematological effects. Both sexes showed clinical chemistry effects at 2000 mg/kg. Males showed absolute and relative weight effects on heart, liver, kidney, adrenals, testes and spleen at ≥ 1000 mg/kg. Females had relative organ weight effects in liver, heart, kidney and spleen at 2000 mg/kg. **NOTE:** No histopathology was performed.) No adverse effect. These data are supplemental. (Kishiyama & Silva, 9/7/95).

Combined Study:

**** 013 093436** "24 Month Dietary Chronic Toxicity and Oncogenicity Study in the Rat", (M. Blair, International Research and Development Corporation, Laboratory Project I.D. 551-005, 9/30/91). MGK* Repellent 326, (purity = 99.4%; Di-n-propyl isocinchomeronate) was fed in diet at 0 (2 controls: A & B), 65, 250, or 1000 mg/kg/day to Charles River CD* rats (60/sex/dose; 60/sex/control for A & B) for 104 weeks. Chronic NOEL = 250 mg/kg/day (Decreased body weight and food consumption were observed in both sexes at 1000 mg/kg. Increased AST in males was observed at 1000 mg/kg. Decreased kidney and heart (both sexes) and adrenal weights (female

only) were observed at 1000 mg/kg.) Oncogenicity NOEL = 250 mg/kg (Increased incidence in hepatocellular and renal cell adenomas and carcinomas, uterine polyps and testicular interstitial cell tumors were observed at 1000 mg/kg.) **Possible adverse effect.** ACCEPTABLE. (Kishiyama & Silva, 9/11/95).

CHRONIC, DOG

Subchronic Study:

008 088194, "Two Month Dietary Range-Finding Toxicity Study in Dogs Using MGK* Repellant 326", (Malcolm Blair, International Research and Development, Laboratory Project I.D. 551-003, 8/29/86). MGK* Repellant 326 (purity = 100%, Lot #: 3716) was administered in the feed at concentrations of 0, 4000, 7500 and 15000 (reduced to 10000 on day 15), 30000 (reduced to 1000 on day 8), or 60000 (reduced to 2000 on day 8) ppm to 2 beagle dogs/sex/group for 2 months. No adverse effects indicated NOEL = 2000 ppm/day (Inappetence, decreased bodyweight and food consumption was observed at ≥ 7500 ppm in both sexes. Decreased alanine aminotransferase activity at 15000/10000 ppm and liver weights at ≥ 7500 ppm were observed. Portal bile duct proliferation and portal fibrosis in liver, correlated with mild centrilobular and hepatocellular atrophy and telangiectasis with depressed surface areas of the liver were observed at ≥ 7500 ppm.) NOAEL = 4000 ppm (no significant effects were observed at ≤ 4000 ppm--slight decrease in weight and slight decrease in food consumption). The data are supplemental. The report suggested that 4000 ppm/day should be the high dose level employed in a definitive study. (Kishiyama & Silva, 1/7/91).

Chronic Study:

** 009 088195, "One Year Dietary Toxicity Study in Dogs", (Malcolm Blair, International Research and Development, IRDC Study 551-006, 9/19/89). MGK* Repellent 326 (100% pure, Lot #: 3716) was administered in the feed at concentrations of 0 (feed), 250, 1000, or 4000 ppm to 4

Beagle dogs/sex/group for 52 weeks. NOEL = 250 ppm (males) based on lower body weights at 4000 ppm (10.8 to 20.9% lower for 49 of 52 weeks) and 1000 ppm (10.2 to 13.4% for 10 of 52 weeks and 9.2 to 9.9% lower for 9 of 52 weeks). NOEL > 4000 ppm for females (No effects observed at any dose.) NOAEL = 4000 ppm (No significant toxic effects were observed at any dose.) ACCEPTABLE. (Kishiyama & Silva, 1/8/91).

ONCOGENICITY, MOUSE

Subchronic Study:

014, 017 111269, 114162 "13 Week Dietary Range-Finding Toxicity Study in Mice", (M. Blair, International Research and Development Corporation, Laboratory Project ID 551-001, 2/4/87 (amended 10/24/91)). MGK* Repellent 326 (99.4% pure) was fed in diet to Charles River CD*-1 mice (10/sex/dose) at 0, 125, 250, 500, 1000 or 2000 mg/kg/day for 13 weeks. NOEL = 500 mg/kg (Body weights were decreased and food consumption was increased in males at \geq 1000 mg/kg. Both sexes showed increased relative liver, brain weights at \geq 1000 mg/kg. Males showed decreased kidney weights at \geq 1000 mg/kg.) Chemical characterization was in volume 017/114162. (Kishiyama & Silva, 9/11/95).

Oncogenicity Study:

**** 015 111269,** "Eighteen Month Dietary Oncogenicity Study in Mice", (M. Blair, International Research and Development Corporation, Laboratory Project ID 551-004, 9/30/91). MGK* Repellent 326 (100.00% pure; Di-n-propyl isocinchomeronate) was mixed with the feed at concentrations of 0 (controls A & B), 125, 500, or 2000 mg/kg/day and fed to 50 Charles River CD*-1 mice/sex/group for 80 weeks (including 50/sex/dose each for controls A & B). Systemic NOEL = 125 mg/kg (There was decreased body weight and increased food consumption was observed in both sexes at \geq 500 mg/kg. Increased liver nodules and masses were observed in both sexes at 2000 mg/kg. Absolute and/or relative liver, brain, kidney, and adrenal weights were

increased at 500 mg/kg in both sexes. Relative testis weights were decreased at 2000 mg/kg. Biliary stasis, portal bile duct proliferation, histiocytosis, portal mononuclear cell infiltration and hepatocellular hypertrophy (males) and gallbladder calculi were observed in both sexes at 2000 mg/kg.) Oncogenic NOEL = 500 mg/kg (Hepatocellular adenomas (females) and carcinomas in both sexes and alveolar bronchiolar adenomas (males) were observed at 2000 mg/kg.) Possible adverse effect. ACCEPTABLE (Kishiyama & Silva, 9/12/95).

REPRODUCTION, RAT

** 010 088586, "Two Generation Reproduction Study of MGK Repellent 326 in the Albino Rat", (J. L. Schardein, International Research and Development, IRDC 551-009, June 7, 1990). MGK* Repellent 326 (purity = 100%, Lot #: 3716) was administered in the feed at concentrations of 0, 65, 250, or 1000 mg/kg/day to 2 generations (with 2 litters/generation) of Sprague-Dawley Charles River COBS* CD* (26/sex/group treated; 2 control groups were used with 26/sex/group). Treatment was initiated at least 80 days before the mating of F₀ parents and at weaning of F_{1b} pups (eventual F₁ parents) and was continued 21 days (end of lactation) after the birth of the 2nd litter for each generation. No adverse effect indicated. Parental NOEL = 250 mg/kg/day (Reduced body weight in both sexes at 1000 mg/kg and mild proliferation of portal bile ducts with increased incidence of trace mononuclear cell infiltrate in the portal areas was observed in F₀ females and both sexes of F₁ at 1000 mg/kg/day.) Reproductive NOEL > 1000 mg/kg/day (no effects were observed at any dose). Pup NOEL = 250 mg/kg/day (Decreased pup weights and body size was observed at 1000 mg/kg.) ACCEPTABLE. (Kishiyama & Silva, 1/9/91).

TERATOLOGY, RAT

Range-finding Study:

011 098175, "MGK* Repellent 326 Rat Teratology Dose Ranging Study", (L.F.H. Irvine, Toxicol Laboratories Limited, Laboratory Project ID MGK/6/R, 11/22/90). MGK* Repellent 326 (Di-n-propyl isocinchomeronate; purity = 98.8%) was administered by gavage at concentrations of 0 (carboxymethylcellulose, 1.0%), 100, 200, 400 or 800 mg/kg/day to 5 mated female Sprague-Dawley rats/group during organogenesis (days 6-15 of gestation). Maternal NOEL \geq 800 mg/kg/day (No effects were observed at any dose). Developmental NOEL = 400 mg/kg/day (reduced fetal weight). Possible adverse effect: Fetal weights were reduced in the absence of maternal toxicity. These data are supplemental and not subject to FIFRA Guidelines. Based upon the results, the treatment range for the definitive study was determined (100, 300 and 1000 mg/kg). The 1000 mg/kg dose level is considered by FIFRA Guidelines to be the maximum limit dose. (Kishiyama & Silva, 9/6/95).

Developmental Study:

** 011 098176, "MGK* Repellent 326 Rat Teratology Study", (L.F.H. Irvine, Toxicol Laboratories Limited, Laboratory Project ID MGK/8/R, 8/1/91). MGK* Repellent 326 (Di-n-propyl isocinchomeronate; purity = 98.8%) was administered by gavage at concentrations of 0 (carboxymethylcellulose, 1.0%), 100, 300, or 1000 mg/kg/day to mated female Sprague-Dawley rats (24/dose) on days 6 through 15 of gestation. **Maternal NOEL = 300 mg/kg/day** (Reduced body weight gain and food consumption were observed at 1000 mg/kg). **Developmental NOEL = 1000 mg/kg** (No effects were observed at any dose.) No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 9/6/95).

004 037753, "Effect of "MGK Repellent 326" (Dipropyl Isocinchomeronate) on the Embryonic Development of Rats After Oral Application", (International Bio-Research, Inc., 12-76). Dipropyl isocinchomeronate, lot no. 1015-3, was given by gavage to pregnant Wistar rats on days 5 to 15 of gestation at dose levels of 0 (peanut oil), 50, 200 or 600 ul/kg. Maternal NOEL > 600 ul/kg; Developmental NOEL = 50 ul/kg (decreased fetal weight). An increase in malformations and variations in ossification are reported, historical controls are needed to determine significance. UNACCEPTABLE (need justification of dose - no evidence of maternal toxicity, no results of visceral exam or historical data are included, no analysis of dosing solutions, no purity stated). NOT UPGRADEABLE. (JR(G), 2-13-86).

001 904659 An 8 page summary and conclusion on report no. 004 37753. There is no worksheet for this report.

TERATOLOGY, RABBIT

** 006 064510, " Teratological Study of MGK Repellent 326 Administered Orally to Albino Rabbits", (International Research and Development Corporation, study no. 551-008, 10/29/87). MGK Repellent 326 (Dipropyl isocinchomeronate), 100% pure, was administered by gavage to 16 New Zealand White SPF rabbits per group at 0 (0.5% methylcellulose), 35, 100 or 350 mg/kg/day during days 7 through 19 of gestation. Treatment related mortality was excessive at the high dose with 15 unscheduled deaths and 1 abortion. Five of the does which developed labored breathing, leaning, and rotating in circles to the left were sacrificed in extremis . The other 9 dead does were reported to have no visible abnormalities. Maternal NOEL = 100 mg/kg/day (high mortality) Developmental NOEL = > 100 mg/kg/day (no adverse effect). The study was reviewed as unacceptable (Gee 7/25/88). Upon review of the pilot study used for dose justification and an analysis of the test compound (both contained in record #070492), the data provided were found adequate to upgrade this main study to ACCEPTABLE status. (Chernoff, 8/15/89)

007 070492 Supplemental information on test article analysis and dose range
determination for the study reported in Record No. 064510.

GENE MUTATION

** 005 063245, "Salmonella/Mammalian Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Associates Inc., Lab. study no: T5204.501014, 9/12/86). Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation; tested at 0 (acetone), 100, 333, 1000, 2500 or 5000 µg/plate, triplicate plates, two trials each strain; no evidence of an increase in reversion rate reported; ACCEPTABLE. (Gee, 7/21/88).

** 005 063248, "L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay", (Microbiological Associates, Inc., Lab. study no: T5204.701020, 12/15/86). Mouse lymphoma cells tested for mutagenicity with MGK Repellent 326, no purity stated; with and without rat liver activation; two trials with activation: Trial one at 0, 0.13, 0.18, 0.24, 0.32, 0.42, 0.56, 0.75, 1.0, 1.3 or 1.8 µl/ml with 1.3 and 1.8 being too toxic to clone. Trial two tested at 0, 0.7, 0.8, 0.9, 1.0, 1.1 or 1.2 µl/ml in duplicate. Two trials without activation: Trial one at 0, 0.05, 0.11, 0.18, 0.24 or 0.31 in duplicate. Trial two tested at 0.024, 0.032, 0.042, 0.056, 0.073, 0.1, 0.13, 0.18, 0.24 or 0.32 µl/ml, single culture per concentration. Results equivocal for biological significance. ACCEPTABLE with no adverse effect. (Gee, 7/22/88).

CHROMOSOME

** 005 063246, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells with a Confirmatory Assay: Final Report", (Microbiological Associates, Inc., Lab. study no: T5204.337001, 1/14/87). MGK Repellent 326, lot 3716, no purity given, clear liquid; Chinese hamster ovary cells, CHO-K₁; tested with and without male Sprague-Dawley Aroclor-induced rat liver activation; duplicate cultures, two trials; without activation, 0 (acetone and medium), 0.02, 0.05, 0.1 and 0.2 µl/ml, with activation, 0 (acetone and medium), 0.1, 0.25, 0.5 or 1.0 µl/ml; concentrations based on a preliminary trial; no consistent increase in chromosomal aberrations reported; ACCEPTABLE. (Gee, 7/22/88).

DNA DAMAGE

** 005 063247, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes: Final Report", (Microbiological Associates, Inc., Lab. study no: T5204.380009, 4/20/87). MGK Repellent 326, no purity stated; tested with primary rat hepatocytes for unscheduled DNA synthesis by autoradiography at 0 (solvent - DMSO or acetone), 0.003, 0.01, 0.02, 0.03 or 0.06 µl/ml, 18 - 20 hour incubation; triplicate cultures with parallel triplicates for cytotoxicity - cytotoxicity determined by release of lactic acid dehydrogenase as a measure of the integrity

of cell membranes; unscheduled DNA synthesis by autoradiography after incubation with ³H-thymidine; no evidence for treatment-related UDS at any concentration; ACCEPTABLE. (Gee, 7/22/88).

NEUROTOXICITY

Not required at this time.